(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 933 079 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
24.03.2004 Bulletin 2004/13

(51) Int Cl.[7]: **A61K 9/20**, C08B 30/12

(21) Application number: **99300571.9**

(22) Date of filing: **26.01.1999**

(54) Free-flowable, directly compressible starch as binder, disintegrant and filler for compression tablets and hard gelatine capsules

Fliessfähige, direktverpressbare Stärke als Bindemittel, Sprengmittel und Füllstoff für Presstabletten und Hartgelatinkapseln

Amidon s'écoulant librement, directement compressible comme liant, désintégrant et charge pour comprimés par compression et capsules en gélatine dure

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI NL PT SE

(30) Priority: **03.02.1998 GB 9802201**

(43) Date of publication of application:
04.08.1999 Bulletin 1999/31

(73) Proprietor: **CERESTAR HOLDING BV**
NL-4550 AA Sas Van Gent (NL)

(72) Inventors:
- **Michaud, Jacques Loic Marie**
  1160 Brussels (BE)
- **Provoost, Dirk Reimond**
  1800 Vilvoorde (BE)
- **Van Bogaert, Elsie**
  2880 Bornem (BE)

(74) Representative: **Knowles, James Atherton**
Stevens Hewlett & Perkins
1 St Augustine's Place
Bristol BS1 4UD (GB)

(56) References cited:
EP-A- 0 130 683
GB-A- 1 216 873
US-A- 3 956 515
US-A- 5 164 014
US-A- 5 560 927

EP 0 933 079 B1

Description

Technical field

[0001] This invention relates to a free-flowing compressible processed starch powder suitable for use both as a binder and as a disintegrant in tablets or capsules and to a process for producing this.

Background of the invention

[0002] Tablets and capsules are amongst the most frequently employed delivery forms for most medicinal preparations. This situation can be explained by the fact that these dosage forms allow a good accuracy of dosage of the active component of the medicinal formulation. Furthermore, as no liquids are generally involved in the process for preparing these medicinal formulations, handling and packaging are a lot easier. Last but not least, conservation and stability of these preparations are generally better than those of other formulations.

[0003] The same arguments also explain the reason why tablets are often used as media for other applications such as food, including confectionery products, aromas or sweeteners, detergents, dyes or phytosanitary products.

[0004] Tablets can be manufactured using three main processes, wet granulation, dry granulation and direct compression.

[0005] In wet granulation, components are typically mixed and granulated using a wet binder, the wet granulates are then sieved, dried and eventually ground prior to compressing the tablets.

[0006] In dry granulation, powdered components are typically mixed prior to being compacted, also called pre-compression, to yield hard slugs which are then ground and sieved before the addition of other ingredients and final compression.

Direct compression is now considered to be the simplest and the most economical process for producing tablets. This process requires only two steps; i.e., the mixing of all the ingredients and the compression of this mixture.

[0007] Hard gelatine capsules are usually filled with their ingredients according to two possible techniques. One uses gravity when these ingredients are poured into the capsule due to their natural flow. The other involves partial compression according to which the ingredients are compressed inside a calibrated punch prior to being deposited into the capsule.

[0008] A component of a tablet or capsule is usually defined as being either an excipient or an active ingredient. Active ingredients are normally ones that trigger a pharmaceutical, chemical or nutritive effect and they are present only up to the strict limit necessary for providing this effect in the right proportion. Excipients are chemically and pharmaceutically inert ingredients which are included to facilitate the preparation of the dosage forms or to adapt the release of the active ingredients.

[0009] Excipients, when intended for direct compression, must fulfil a certain number of properties. They should have a high flowability. They should have a high compressibility, a good pressure-hardness profile. They should be compatible with all types of active ingredients and not interfere with their biological availability, they also should be stable against ageing, air moisture and heat. They should be colourless and tasteless. And finally they should possess proper mouthfeel.

[0010] Excipients can be characterised according to their function during the formulation as, for instance, binders, disintegrants, fillers (or diluents), glidants, lubricants and eventually flavours, sweeteners and dyes.

[0011] Lubricants are intended to improve the ejection of the compressed tablet from the die of the tablet-making equipment or from the punches used for compressing ingredients for introduction into capsules.

[0012] Glidants are added to improve the powder flow. They are typically used to help the mixture of all the components to fill evenly and regularly the die before the compression.

[0013] Fillers are inert ingredients sometimes used as bulking agents in order to decrease the concentration of the active ingredient in the final formulation. The function of filler may, in some cases, be also provided by the binder.

[0014] Disintegrants may be added to formulations in order to help the tablets disintegrate when they are placed in a liquid environment and so release the active ingredient. The disintegration properties are, mostly, based upon the ability of the disintegrant to swell in the presence of a fluid, such as water or gastric juice. This swelling disrupts the continuity of the tablet structure and thus, allows the different components to enter into solution or into suspension. Commonly used disintegrants include native starches, modified starches, modified celluloses, microcrystalline cellulose or alginates.

[0015] Binders are used to hold together the structure of the dosage forms. They have the property to bind together all the other ingredients after sufficient compression forces have been applied and they provide the integrity of the tablets. Commonly used compression binders include pregelatinised starches, polyvinylpyrrolidone, methylcellulose, microcrystalline cellulose, sucrose, lactose, dextrose, sorbitol or mannitol.

[0016] Starches are known to act in some cases as binders and in some other cases as disintegrants according to

the fact that they are native, chemically modified or physically modified.

[0017] Native granular starches and, to a smaller extent, cooked starches (also referred to as pregelatinised starches) can show somewhat limited binding capacities when employed in direct compression. Cooked starches, even when they are satisfactory as binders are not satisfactory in terms of disintegration. These starches do not really disperse, they show the tendency to prevent the penetration of water into the tablet, thus preventing its disintegration, by forming a tacky film on its surface.

[0018] EP-A-0402186 describes a directly compressible starch mixture obtained by mixing 1 to 20% of a starch paste with 99-80% of native starch. The starch paste is obtained by treating native starch at 85°C which results in breaking of the starch granules.

[0019] Partially cold water swellable starches for use as binders and/or disintegrants in the manufacture of tablets by direct compression and as fillers for formulations supplied in hard gelatine capsules, are described in US-A-3,622,677 and US-A-4,072,535. The material described is essentially a pre-compacted starch powder obtained by subjecting a non-gelatinised granular starch to physical compaction between steel rollers with the possible input of thermal energy. The compacted starch shows the presence of sharp birefringent granules and non-birefringent granules as well as some aggregates of granules and fragments dried to a moisture content of 9-16%. After the compactation the starch is ground and sieved to yield a free flowing powder. The above mentioned starch powders exhibit limited binding capacity in direct compression and poor disintegration properties. Formulations of active ingredients prepared using that kind of excipient are described, for instance in EP-A-0,130,683 for N-acetyl-p-aminophenol.

[0020] Other cold water swellable physically modified starches are described as being useful as disintegrant but with very poor binding properties (see US-A-4,383,111). In that case, the granular starch is cooked in the presence of water and possibly an organic solvent at a temperature not higher than 10°C higher than its gelatinisation temperature. The so-obtained starch is then dried resulting in non-birefringent granules. Mixtures containing cold water swellable starch are described for food application i.e. US-A-3,956,515, for the preparation of starch batter for meet pieces.

[0021] Chemical modification of starch has also been investigated. Crosslinked pregelatinised starches such as starch phosphates, starch adipates, starch sulphates, starch glycolates or carboxymethyl starches are useful as disintegrants although they exhibit poor binding capacities (see US-A-3,034,911 and US-A-4,369,308).

[0022] Acid and enzyme hydrolysed starches are reported to be useful as binders (US-A-4,551,177). These compressible starches are prepared by treating a granular starch with an acid and/or alpha-amylase enzyme at a temperature below the gelatinisation temperature of the starch. These treated starches show altered and weakened granules with disrupted surfaces. These starches are said to be useful as binders for tabletting as well as binders and fillers for capsule filling and are said to exhibit reasonable disintegration properties.

[0023] Dextrinised starches (see US-A-4,384,005) and starch fractions such as non-granular amylose (see US-A-3,490,742) are also described as having limited binding and/or disintegration properties. These are of limited interest due to the expensive processes needed for their preparation.

[0024] It appears clearly that there is a need for a free-flowing directly compressible starch powder showing both an excellent compression profile and very good disintegration properties and which is neither chemically modified nor chemically or enzymatically treated and without the use of an organic solvent.

Summary of the invention

[0025] According to the present invention, there is provided a free-flowing directly compressible processed starch powder characterised in that it comprises regular and smooth partially-swollen granules of starch wherein the ratio of non-swollen birefringent granules to swollen non-birefringent granules is in the range of from 1:5 to 5:1 and in that it has an average particle size greater than 50 μm and a moisture content of from 3 to 15% by weight, and wherein when compressed into a tablet under a compression force of 10 kN, said free-flowing directly compressible processed starch powder gives a tablet having a Tensile Strength of at least 1 N/mm^2.

[0026] The processed starch powder according to the invention is suitable for use as a binder in direct compression processes yielding very hard tablets at relatively low compression forces as well as suitable for use as a binder and/or filler in the preparation of capsule dosage forms. Tablets resulting from the compression of the above-mentioned starch disintegrate in an aqueous medium at a high speed and, additionally, exhibit a low friability pattern.

Detailed description of the invention

[0027] The starch powder of the invention is characterised by regular and smooth either birefringent or non-birefringent partially swollen granules. The ratio between non-swollen birefringent granules and swollen non-birefringent granules can vary from 1:5 to 5:1, preferably from 1:2 to 2:1, and is typically preferred to be around 1:1, as characterised by polarised optical microscopy. The particle size of the free-flowing direct compressible starch powder is noticeably bigger than that of the raw material starch and has an average value greater than 50μm, typically from 50 to 500μm

(about 95µm in the case of maize starch). Further agglomeration of granules is also possible in order to increase particle size and to adapt the flow of the powder.

[0028] According to the present invention there is provided a process for preparing a free-flowing compressible starch powder comprising the steps; 1) preparing a slurry of starch in water, 2) heating the slurry to a temperature not substantially higher than the gelatinisation temperature of the starch to cause partial swelling of the starch granules without causing disruption of the starch granules, 3) cooling the starch slurry to prevent any further swelling of the starch granules and 4) spray-drying the cooled slurry to produce a free-flowing starch powder having a moisture content of from 3 to 15% by weight.

[0029] Suitable free-flowing direct compressible starch powder can be obtained either by diluting the starch base powder in demineralised water in order to form a slurry at a concentration of from 10 and 40%, calculated on dry substance basis, or by using a starch slurry resulting from the process applied to any relevant starch containing plant (slurry of a concentration of 20% is preferred as being a good compromise between the workability of the product and the economical viability of the process).

The starch slurry is then heated at a temperature close to the gelatinisation temperature of the starch used such that starch granules start swelling without being disrupted and solubilised in the water. This temperature depends upon the plant source. For maize starch this is typically around 62° C although starches from other sources will require different heating temperatures. We have found that a starch slurry heated to a temperature of more than 5°C higher than the gelatinisation temperature of the starch used will result in a viscous paste that cannot be processed further in an aqueous medium according to the process of the present invention. Therefore, a relatively strict control of the temperature within a range of ±5°C of the gelatinisation temperature of the starch used is important. Preferably, the temperature to which the starch slurry is heated is controlled to within a range of ±3°C, and more preferably within the range of ±1°C, of the gelatinisation temperature of the starch used. The temperature will depend on the type of starch used. The aim always is to obtain a starch which is partially birefringent and partially non-birefringent. The residence time in the heating device can vary from 30 sec. to 10 min. and is typically around 1 min. The heating device can be any heat exchanger, although a direct steam injection heater is preferred because it allows a better control of the temperature and the residence time. After heating the partially swollen starch slurry is cooled, typically to a temperature 5-15° C lower than the heating temperature, in order to stabilise the product and to prevent further swelling or bursting of starch granules. Preferably a reduction of 6-7° C in the temperature is applied. The stabilised slurry is then spraydried using a spray-drying tower equipped either with nozzles or with turbines. Inlet and outlet temperatures are controlled such that the final free-flowing direct compressible starch powder has a moisture content of 3-15%, preferably 5-10% depending upon pharmaceutical dosage forms in the use of which this free-flowing direct compressible starch is intended.

[0030] The free-flowing direct compressible starch powder of the invention can be derived from any starch-containing plant source. This includes maize (either normal maize or hybrids such as white maize, waxy maize and high-amylose containing maizes), wheat, potato, rice, sorghum, tapioca, cassava and any other similar starch-containing plants. White maize and high-amylose starches are preferred because of the better characteristics of the final products as described in the following examples.

[0031] The free-flowing direct compressible starch powder of the invention is useful as a binder and/or a disintegrant for tablets prepared by direct compression, wet granulation or dry granulation. It is also useful as a binder and a filler in the process of filling capsules.

[0032] A further embodiment of the present invention comprises a composition for the formulation of capsules and tablets prepared either by direct compression or, to a smaller extent by dry or wet granulation, containing the above-mentioned starch powders referred to as free-flowing directly compressible starch powders together with at least one active material.

[0033] The free-flowing compressible processed starch described in this invention can be used to formulate any drug usually delivered in tablet or capsule forms. This includes for instance analgesics, antipyretics, anti-inflammatory agents, vitamins, antibiotics, hormones, steroids, tranquillisers, or sedatives. Other active materials that can be included into tablets can also be formulated with the free-flowing compressible processed starch described in this invention. This triggers applications such as food, including confectionery products, aromas or sweeteners, detergents, dyes, fertilisers or herbicidal products.

[0034] Tablets obtained using the free-flowing directly compressible starch powders of the present invention as binder and disintegrant are characterised by the fact that they show very high hardness at relatively low compression forces whilst they are also capable of disintegrating in an aqueous medium at a high speed, and additionally exhibit a low friability pattern. Free-flowing directly compressible starch powders of the present invention, can be used as binder-disintegrant either alone or in conjunction, at any useful ratio, with any other binders and or disintegrants. Useful dosage of the free-flowing directly compressible starch powders of the invention varies depending upon active ingredients and other excipients and can be comprised from 2 to 95%.

The figures are attached to help the understanding of the nature of the treatments applied to the starch during the process.

[0035] **Fig. 1** shows a partially swollen white maize starch processed at 61 °C (by polarised optical microscopy). It shows the presence of a majority of non-swollen birefringent granules and a minority of swollen non-birefringent granules.

[0036] **Fig. 2** shows a partially swollen white maize starch processed at 62°C (by polarised optical microscopy). It shows the presence of more or less the same number of non-swollen birefringent granules and swollen non-birefringent granules.

[0037] **Fig. 3** shows a partially swollen white maize starch processed at 63°C (by polarised optical microscopy). It shows the presence of a minority of non-swollen birefringent granules and a majority of swollen non-birefringent granules.

[0038] **Fig. 4** shows native white maize starch granules by scanning electron microscopy.

[0039] **Fig. 5** shows a free-flowing directly compressible starch based on white maize granular starch according to the invention exemplified in Example 1 by scanning electron microscopy. Big and smooth granules can easily be identified.

EXAMPLE 1

[0040] This example describes the production of a free-flowing directly compressible starch powder based on a granular white maize starch hybrid. The granular white maize starch powder was diluted in demineralised water in order to form a slurry at a concentration of 20% calculated on dry substance resulting in a slurry with a relative density of 1.085 compared to water. The starch slurry was then heated in a direct steam injection heat exchanger at a temperature of 62° C with a variation of no more than ±1° C. If the temperature reached 64°C, a viscous paste was obtained which could not be processed further. Microscopic examination of such a paste revealed the absence of birefringent granules. The heating time was maintained for a time of 1 minute. The partially swollen starch slurry was then cooled down to a temperature of 55-57°C by cold water. Drying of the cooled partially swollen starch slurry was carried out using a Alfa-Laval spray-drying tower equipped with a turbine turning at a maximum speed of 13,000 rd/min and fed at 2.7-3.1 m^3/h. The inlet temperature was fixed at 252°C and the outlet temperature was fixed at around 81°C in order to obtain a product with a final dry substance of around 91 %. The intense white free-flowing powder obtained as described showed an average particle size of 95 µm compared to 20 µm for the initial granular white maize starch as shown in Table 1.

TABLE 1

Starch	1-10 µm	10-25 µm	25-50 µm	50-75 µm	75-100 µm	100-125 µm	125-150 µm	150-200 µm	200-300 µm	loose density
Native (%)	12.5	80.1	6.5	0.7	0.2	0	0	0	0	500 g/l
Processed (%)	0.3	8.3	18.2	16.3	19.4	10	12.5	9	6.0	510 g/l

[0041] As shown in Table 1, the above described free-flowing directly compressible starch is characterised by a particle size noticeably bigger than that of the raw material starch typically centred on 95 micrometers. As seen by polarised microscopy (see Figures 1 to 3), swelling of starch granules depends very much on the heating temperature of the slurry. A heating temperature of 61-62°C produces granules with a typical ratio between non-swollen birefringent granules and swollen non-birefringent granules of around 50/50 (Figures 1 and 2). A heating temperature of 63°C results in a product showing a much smaller proportion swollen non-birefringent granules (Figure 3).

EXAMPLE 2

[0042] This example describes the production of a free-flowing directly compressible starch powder based on a granular high-amylose maize starch hybrid. The granular high-amylose maize starch powder was diluted in demineralised water in order to form a slurry at a concentration of 20% calculated on dry substance resulting in a slurry with a relative density of 1.050 compared to water. The starch slurry was then heated in a direct steam injection heat exchanger at a temperature of 78°C with a variation of no more than ±2°C. The heating was maintained for a time of 1 minute. The partially swollen starch slurry was then cooled down to a temperature of 50°C by cold water. Drying of the cooled partially swollen starch slurry was carried out using a Niro FSD 4 spray-drying tower equipped with nozzles and fed at 10 litre/h.. The inlet temperature was fixed at 200°C and the outlet temperature was fixed at around 80°C in order to obtain a product with a final dry substance of around 91%.

[0043] The free-flowing powder of high amylose starch obtained as described showed an average particle size of 85 µm compared to 20 µm for the initial granular high-amylose maize as shown in Table 2.

TABLE 2

Starch	1-10 µm	10-25 µm	25-50 µm	50-75 µm	75-100 µm	100-125 µm	125-150 µm	150-200 µm	200-300 µm	loose density
Native (%)	12.5	80.1	6.5	0.7	0.2	0	0	0	0	500 g/l
Processed (%)	0.9	6.9	18.1	20.6	25.2	10.9	7.4	6.3	3.7	300 g/l

As shown in Table 2, the above described free-flowing directly compressible starch is characterised by a particle size noticeably bigger than that of the raw material starch typically centred on 85 micrometers.

EXAMPLE 3a

[0044] This example demonstrates the advantages of directly compressible free-flowing starches obtained as described in Example 1 and Example 2 compared to conventional compressible starches when used for the production of tablets by direct compression. Tablets were formulated with 98.8% starch, 1% magnesium stearate Ph.Eur.III (Tramedico) and 0.2% silicon dioxide (Aerosil 200 - Degussa). The starch was sieved over a 0.8mm sieve and blended with silicon dioxide for 15 min. at 12 rpm. in a low-shear drum mixer. Magnesium stearate was added to the mix and blended for 3 min. at 12 rpm. All tabletting trials were performed on a triple punch rotary Korch tabletting press at a speed of 40 rpm to produce 1 cm^2 flat faced tablets of a weight of 350 mg. Hardness and dimensions of tablets were measured on a PharmaTest PTB-311 tablet-test unit. The disintegration time of tablets was determined on a PharmaTest PTZ-E in water at 37°C. The friability was measured on a PharmaTest PTF-E friabilator. All tests were performed according to the procedures described in European Pharmacopoeia 3rd edition. The tensile strength (TS) was calculated from the hardness according to the formula $TS = 2.H / \Pi.D.T$ where H is the hardness of the tablet, D is the diameter and T is the thickness. The results are summarised as shown in Tables 3 to 5.

TABLE 3

	Tensile strength (N/mm^2)					
Compression force (kN)	5	10	15	20	25	30
Processed white maize *	0.4	1.6	2.6	3.2	3.5	3.6
Processed high-amylose **	1.7	4.1	5.6	6.5	6.8	7
Starch 1500™ (Colorcon) ***	0.2	0.5	1	1.3	1.5	1.6

* Free-flowing white maize starch produced as described in Example 1

** Free-flowing high-amylose maize starch produced as described in Example 2

*** Starch 1500™ standard (high) moisture from Colorcon Company

[0045] Table 3 shows clearly that the hardness, directly indicated by tensile strength measurements, of tablets obtained by direct compression of the free-flowing white maize starch produced according to the process described in Example 1 and, to an even bigger extent, the hardness of tablets obtained by direct compression of the free-flowing high-amylose maize starch produced according to the process described in Example 2, are more than significantly higher than that of a standard compressible starch at any compression forces. This fact which directly results from the high binding capacity of the above mentioned starches allows the manufacture of tablets of similar hardness at lower compression forces resulting in significant advantages in the course of the tabletting process.

TABLE 4

	Disintegration time (min.)					
Compression force (kN)	5	10	15	20	25	30
Processed white maize *	1.8	3.8	5.9	6.6	7.1	7.1
Processed high-amylose **	1.5	3.5	5	6	6.5	7
Starch 1500™ (Colorcon)***	10.7	15	25	30	no disint	no disint

* Free-flowing white maize starch produced as described in Example 1

** Free-flowing high-amylose maize starch produced as described in Example 2

*** Starch 1500™ standard (high) moisture from Colorcon Company

[0046] Table 4 shows clearly that the disintegration times of tablets obtained by direct compression of the free-flowing white maize starch produced according to the process described in Example 1 and of tablets obtained by direct compression of the free-flowing high-amylose maize starch produced according to the process described in Example 2, are in the range of being five times smaller than that of a standard compressible starch at any compression forces. This results in significant advantages for the delivery of the active ingredients formulated with the above mentioned starches.

TABLE 5

	Friability (%)					
Compression force (kN)	5	10	15	20	25	30
Processed white maize *	2.5	0.3	0.2	0.1	0.1	0.1
Processed high-amylose **	0.3	0.1	<0.1	<0.1	<0.1	<0.1
Starch 1500™ (Colorcon)***	4.5	3.2	1.2	0.8	0.7	-

* Free-flowing white maize starch produced as described in Example 1

** Free-flowing high-amylose maize starch produced as described in Example 2

*** Starch 1500™ standard (high) moisture from Colorcon Company

[0047] Table 5 shows that even though they have much better disintegration times, at any compression force, the tablets obtained by direct compression of the free-flowing white maize starch produced according to the process described in Example 1 and the tablets obtained by direct compression of the free-flowing high-amylose maize starch produced according to the process described in Example 2, have friability patterns significantly lower than that of the standard compressible starch. Therefore, handling and processing of tablets obtained using above mentioned starches are easier and safer.

[0048] As a conclusion it can be stated that tablets obtained using free-flowing directly compressible starches produced according to Examples 1 and 2 as binders and disintegrants are characterised by high hardness at relatively low compression forces whilst they are also capable of disintegrating in an aqueous medium at a very high speed, and additionally exhibit a low friability pattern.

EXAMPLE 3b

[0049] This example reproduces the same experiments as in example 3a using a different formulation for the tablets. Tablets were formulated with 99.25% starch, 0.5% magnesium stearate Ph. Eur. III (Tramedico) and 0.25% silicon dioxide (Aerosil 200 - Degussa). Hardness and dimensions of tablets were measured on an Erweka TBH 30 MD tablet-test unit. The disintegration time of tablets was determined on a PharmaTest PTZ-E in water at 37°C. The friability was measured on a PharmaTest PTF-E friabilator. All tests were performed according to the procedures described in European Pharmacopoeia 3rd edition. The tensile strength (TS) was calculated from the hardness according to the formula $TS = 2.H / \Pi.D.T$ where H is the hardness of the tablet, D is the diameter and T is the thickness. The results are summarised as shown in Tables 6 to 8.

TABLE 6

	Tensile strength (N/mm^2)					
Compression force (kN)	5	10	15	20	25	30
Processed white maize *	0.5	2.4	4.2	5.5	6.2	6.6
Processed high-amylose **	1.9	4.4	6.9	8.8	10.3	-
Starch 1500™ (Colorcon)***	-	0.7	1.2	1.9	2.3	2.5

* Free-flowing white maize starch produced as described in Example 1

** Free-flowing high-amylose maize starch produced as described in Example 2

*** Starch 1500™ standard (high) moisture from Colorcon Company

TABLE 7

	Disintegration time (min.)					
Compression force (kN)	5	10	15	20	25	30
Processed white maize *	1.5	4	6	7.5	8	9
Processed high-amylose **	2	3	-	5	-	6.5
Starch 1500™ (Colorcon) ***	-	17	25	-	30	40

* Free-flowing white maize starch produced as described in Example 1

** Free-flowing high-amylose maize starch produced as described in Example 2

*** Starch 1500™ standard (high) moisture from Colorcon Company

TABLE 8

	Friability (%)					
Compression force (kN)	5	10	15	20	25	30
Processed white maize *	1.58	0.17	0.09	0.06	0.06	0.06
Processed high-amylose **	0.19	0.08	0.04	0.06	0.02	0.04
Starch 1500™ (Colorcon)***	-	2.73	1.07	0.55	0.4	0.28

* Free-flowing white maize starch produced as described in Example 1

** Free-flowing high-amylose maize starch produced as described in Example 2

*** Starch 1500™ standard (high) moisture from Colorcon Company

[0050] This example shows that when the formulation is optimised compared with example 3a, the increase of performance in terms of tensile strength is even better with the direct compressible starch than with the standard direct compressible starch.

EXAMPLE 4

[0051] This example describes the behaviour of directly compressible free-flowing white maize starch powder obtained as described in example 1 when used for the preparation of tablets by wet granulation. The granulation of the starch was performed in a Collette GRAL 75 high shear mixer. 16 kg of starch were granulated with 3 kg of water for 10 min. The granulates were dried in a fluid bed dryer to 10% moisture. Tablets were formulated with 99.25% granulated starch, 0.5% magnesium stearate Ph. Eur. III (Tramedico) and 0.25% silicon dioxide (Aerosil 200 - Degussa). The granulated starch was blended with silicon dioxide for 15 min. at 12 rpm. in a low-shear drum mixer. Magnesium stearate was added to the mix and blended for 3 min. at 12 rpm. All tabletting trials were performed on a triple punch rotary Korsch tabletting press at a speed of 40 rpm to produce 1 cm^2 flat faced tablets of a weight of 350 mg. Hardness and dimensions of tablets were measured on a Erweka TBH 30 MD tablet-test unit. The disintegration time of tablets was determined on a PharmaTest PTZ-E in water at 37°C. The friability was measured on a PharmaTest PTF-E friabilator. All tests were performed according to the procedures described in European Pharmacopoeia 3rd edition. The tensile strength (TS) was calculated from the hardness according to the formula $TS = 2.H / \Pi.D.T$ where H is the hardness of the tablet, D is the diameter and T is the thickness. The results are summarised as shown in Tables 9.

TABLE 9

Compression force (kN)	5	10	15	20	25	30
Tensile strength (N/mm^2)	0.45	2.2	4	5.5	6	6.5
Disintegration time (min.)	0.5	2	2.5	3.6	4.2	5.2
Friability (%)	2	0.22	0.17	0.17	0.12	0.1

[0052] The results show that the tensile strengths of the tablets obtained after wet granulation are very similar to those of tablets obtained by direct compression as listed in example 3b. This demonstrates the suitability of the directly compressible starch described in this invention for the preparation of tablets by wet granulation.

EXAMPLE 5

[0053] This example demonstrates the advantage of directly compressible free-flowing white maize starch powder obtained as described in Example 1 compared to a conventional compressible starch when used for the production of aspirin (Merck USP) tablets by direct compression. Tablets were formulated with 19.3% starch, 80% aspirin, 0.5% magnesium stearate Ph.Eur.III (Tramedico) and 0.2% silicon dioxide (Aerosil 200 - Degussa). The starch and aspirin were sieved over a 0.8mm sieve and blended together with the silicon dioxide and the magnesium stearate for 15 min. at 12 rpm. in a low-shear drum mixer. All tabletting trials were performed on a triple punch rotary Korsh tabletting press at a speed of 40 rpm to produce 1 cm^2 tablets of a weight of 450 mg. Hardness and dimensions of tablets were measured on a PharmaTest PTB-311 tablet-test instrument. The disintegration time of tablets was determined on a PharmaTest PTZ-E in water at 37°C. The friability of the tablets was measured on a PharmaTest PTF-E friabilator. All tests were performed according to the procedures described in European Pharmacopoeia 3rd edition. The tensile strength (TS) was calculated from the hardness according to the formula $TS = 2.H / \Pi.D.T$ where H is the hardness of the tablet, D is the diameter and T is the thickness. The results are summarised as shown in Table 10.

TABLE 10

Compression force (kN)	15	20	25	30
	Tensile strength (N/mm^2)			
Aspirin + Processed white maize *	1.25	1.5	1.6	1.65
Aspirin + Starch 1500™ (Colorcon)**	0.7	0.8	0.9	0.95
	Disintegration time (min.)			
Aspirin + Processed white maize *	1.25	2	2.9	3
Aspirin + Starch 1500™ (Colorcon)**	7	10	11	12.5
	Friability (%)			
Aspirin + Processed white maize *	0.8	0.62	0.55	0.52
Aspirin + Starch 1500™ (Colorcon)**	1.75	1.4	1.2	1.25

* Free-flowing white maize starch produced as described in Example 1

** Starch 1500™ standard (high) moisture from Colorcon Company

[0054] Table 6 shows clearly that the hardness, directly indicated by tensile strength, of tablets obtained by direct compression of aspirin plus the free-flowing white maize starch produced according to the process described in Example I as binder-disintegrant is significantly higher than that of a standard compressible starch at any compression force. This fact which directly results from the high binding capacity of the above mentioned starches allows the manufacture of tablets of similar hardness at lower compression forces resulting in significant advantage in the course of the tabletting process. It also demonstrates clearly that the disintegration times are in the range of being four to five times smaller resulting in significant advantages for the delivery of aspirin so formulated. Another advantage of formulating aspirin with the free-flowing white maize starch produced according to the process described in Example 1 as binder-disintegrant resumes in a significantly lower friability resulting in easier and safer handling and processing of tablet.

[0055] As a conclusion it can be stated that formulating active ingredients such as aspirin in tablets by direct compression using free-flowing directly compressible starch produced according to Example 1 as binder-disintegrant results in tablets of higher hardness, lower disintegration times and lower friability profiles at relatively lower compression forces.

EXAMPLE 6

[0056] This example describes the behaviour of directly compressible free-flowing white maize starch powder obtained as described in when used for the production of ibuprofen (Knoll) tablets by direct compression. Tablets were formulated with 59.25% starch, 40% ibuprofen, 0.5% magnesium stearate Ph. Eur. III (Tramedico) and 0.25% silicon dioxide (Aerosil 200 - Degussa). The starch and ibuprofen were sieved over a 0.8mm sieve and blended together with the silicon dioxide and the magnesium stearate for 15 min. at 12 rpm. in a low-shear drum mixer. All tabletting trials were performed on a triple punch rotary Korsch tabletting press at a speed of 40 rpm to produce 1 cm^2 tablets of a weight of 450 mg. Hardness and dimensions of tablets were measured on a Erweka TBH 30 MD tablet-test unit. The disintegration time of tablets was determined on a PharmaTest PTZ-E in water at 37°C. The friability was measured on a PharmaTest PTF-E friabilator. All tests were performed according to the procedures described in European Pharmacopoeia 3rd edition. The tensile strength (TS) was calculated from the hardness according to the formula $TS = 2.H / \Pi.D.T$ where H is the hardness of the tablet, D is the diameter and T is the thickness. The properties of tablets containing 40% ibuprofen formulated with the free-flowing white maize starch produced as described in Example 1 are summarised in Table 11.

TABLE 11

Compression force (kN)	5	10	15	20	25	30
Tensile strength (N/mm^2)	0.45	1.25	1.6	1.75	1.7	1.7
Disintegration time (min.)	1.1	3.8	-	4.9	-	6.1
Friability (%)	2.4	0.9	0.7	0.8	0.8	0.8

EXAMPLE 7

[0057] This example describes the behaviour of directly compressible free-flowing white maize starch powder obtained as described in when used for the production of paracetamol (Merck USP) tablets by direct compression. Tablets were formulated with 59.25% starch, 40% paracetamol, 0.5% magnesium stearate Ph. Eur. III (Tramedico) and 0.25% silicon dioxide (Aerosil 200 - Degussa). The starch and paracetamol were sieved over a 0.8mm sieve and blended together with the silicon dioxide and the magnesium stearate for 15 min. at 12 rpm. in a low-shear drum mixer.

[0058] All tabletting trials were performed on a triple punch rotary Korsch tabletting press at a speed of 40 rpm to produce 1 cm^2 tablets of a weight of 450 mg. Hardness and dimensions of tablets were measured on a Erweka TBH 30 MD tablet-test unit. The disintegration time of tablets was determined on a PharmaTest PTZ-E in water at 37°C. The friability was measured on a PharmaTest PTF-E friabilator. All tests were performed according to the procedures described in European Pharmacopoeia 3rd edition. The tensile strength (TS) was calculated from the hardness according to the formula $TS = 2.H / \Pi.D.T$ where H is the hardness of the tablet, D is the diameter and T is the thickness. The properties of tablets containing 40% paracetamol formulated with the free-flowing white maize starch produced as described in Example 1 are summarised in Table 12.

TABLE 12

Compression force (kN)	5	10	15	20	25	30
Tensile strength (N/mm^2)	-	0.6	1.2	1.6	1.9	2.1
Disintegration time (min.)	0.85	1.2	-	21	-	2.9
Friability (%)	-	2	0.76	0.48	0.38	0.32

EXAMPLE 8

[0059] This example describes the behaviour of directly compressible free-flowing white maize starch powder obtained as described in when used for the production of ascorbic acid (Merck USP) tablets by direct compression. Tablets were formulated with 59.25% starch, 40% ascorbic acid, 0.5% magnesium stearate Ph. Eur. III (Tramedico) and 0.25% silicon dioxide (Aerosil 200 - Degussa). The starch and ascorbic acid were sieved over a 0.8mm sieve and blended together with the silicon dioxide and the magnesium stearate for 15 min. at 12 rpm. in a low-shear drum mixer.

[0060] All tabletting trials were performed on a triple punch rotary Korsch tabletting press at a speed of 40 rpm to produce 1 cm^2 tablets of a weight of 450 mg. Hardness and dimensions of tablets were measured on a Erweka TBH 30 MD tablet-test unit. The disintegration time of tablets was determined on a PharmaTest PTZ-E in water at 37°C. The friability was measured on a PharmaTest PTF-E friabilator. All tests were performed according to the procedures described in European Pharmacopoeia 3rd edition. The tensile strength (TS) was calculated from the hardness according to the formula $TS = 2.H / \Pi.D.T$ where H is the hardness of the tablet, D is the diameter and T is the thickness. The properties of tablets containing 40% ascorbic acid formulated with the free-flowing white maize starch produced as described in Example 1 are summarised in Table 13.

TABLE 13

Compression force (kN)	5	10	15	20	25	30
Tensile strength (N/mm^2)	-	0.5	1.3	1.8	2.2	2.5
Disintegration time (min.)	0.75	1.5	-	3.8	-	5.6
Friability (%)	-	-	-	-	0.34	-

Claims

1. A free-flowing directly compressible processed starch powder **characterised in that** it comprises regular and smooth partially-swollen granules of starch wherein the ratio of non-swollen birefringent granules to swollen non-birefringent granules is in the range of from 1:5 to 5:1 and **in that** it has an average particle size greater than 50 µm and a moisture content of from 3 to 15% by weight, and wherein when compressed into a tablet under a compression force of 10 kN, said free-flowing directly compressible processed starch powder gives a tablet having a Tensile Strength of at least 1 N/mm^2. --

2. A free-flowing compressible processed starch powder according to claim 1, wherein the tablet has a Tensile Strength of at least 2 N/mm^2.

3. A free-flowing compressible processed starch powder according to either claim 1 or claim 2, wherein the ratio of non-swollen birefringent granules to partially swollen non-birefringent granules is in the range of from 1:2 to 2:1.

4. A free-flowing compressible processed starch powder according to any one of the preceding claims, wherein the ratio of non-swollen birefringent granules to partially swollen non-birefringent granules is about 1:1.

5. A free-flowing compressible processed starch powder according to any one of the preceding claims, wherein at least 50% of the particles have a particle size of 50 μm or greater, preferably 75 μm or greater.

6. A process for preparing a free-flowing compressible starch powder comprising the steps: 1) preparing a slurry of starch in water, 2) heating the slurry to a temperature not substantially higher than the gelatinisation temperature of the starch to. cause partial swelling of the starch granules without causing disruption of the starch granules, 3) cooling the starch slurry to prevent any further swelling of the starch granules and 4) spray-drying the cooled slurry to produce a free-flowing starch powder having a moisture content of from 3 to 15% by weight.

7. A process according to claim 6, wherein the slurry is heated to a temperature which is ±5°C of the gelatinisation temperature of the starch, preferably ±1°C of the gelatinisation temperature of the starch.

8. A process according to either claim 6 or claim 7, wherein the starch slurry after the heating step is cooled to a temperature which is 5° to 15°C lower than the temperature used in the heating step.

9. A composition for forming a tablet or other unit dosage form comprising at least one active material and, as binder or flier, a free-flowing directly compressible processed starch powder of any one of claims 1 to 5.

10. A composition according to claim 9, wherein the active material is selected from the group consisting of pharmaceutically active materials, foodstuffs, including confectionery products, aromas or sweeteners, detergents, enzymes and other proteins, dyes, fertilisers and herbicidal products.

11. A dry compressed tablet comprising at least one active material and, as binder or filler, processed starch, said processed starch comprising regular and smooth partially swollen granules of starch wherein the ratio of non-swollen birefringent granules to swollen non-birefringent granules is in the range of from 1:5 to 5:1 and having an average particle size greater than 50 μm and a moisture content in the range of from 3 to 15% by weight, said tablet, when formed under a compression force of 15 kN, having a Tensile Strength greater than 2 N/mm^2, preferably greater than 3 N/mm^2 and more preferably greater than 4 N/mm^2, a disintegration time in water at 37°C of less than 6 minutes and % friability of less than 1%.

Patentansprüche

1. Rieselfähiges, direkt verpressbares verarbeitetes Stärkepulver, **dadurch gekennzeichnet, dass** es regelmäßige und glatte partiell gequollene Granalien aus Stärke umfasst, wobei das Verhältnis von nicht-gequollenen doppelbrechenden Granalien zu gequollenen nicht-doppelbrechenden Granalien im Bereich von 1:5 bis 5:1 liegt, und dadurch, dass es eine durchschnittliche Teilchengröße von mehr als 50 μm und einen Feuchtigkeitsgehalt von 3 bis 15 Gewichts-% aufweist, und wobei, wenn es unter einer Kompressionskraft von 10 kN zu einer Tablette verpresst wird, das rieselfähige direkt verpressbare verarbeitete Stärkepulver eine Tablette mit einer Zugfestigkeit von mindestens 1 N/mm^2 ergibt.

2. Rieselfähiges verpressbares verarbeitetes Stärkepulver nach Anspruch 1, wobei die Tablette eine Zugfestigkeit von mindestens 2 N/mm^2 aufweist.

3. Rieselfähiges verpressbares verarbeitetes Stärkepulver nach Anspruch 1 oder Anspruch 2, wobei das Verhältnis von nicht-gequollenen doppelbrechenden Granalien zu partiell gequollenen nicht-doppelbrechenden Granalien im Bereich von 1:2 bis 2:1 liegt.

4. Rieselfähiges verpressbares verarbeitetes Stärkepulver nach irgendeinem der vorangehenden Ansprüche, wobei das Verhältnis von nicht-gequollenen doppelbrechenden Granalien zu partiell gequollenen nicht-doppelbrechenden Granalien etwa 1:1 beträgt.

5. Rieselfähiges verpressbares verarbeitetes Stärkepulver nach irgendeinem der vorangehenden Ansprüche, wobei mindestens 50% der Teilchen eine Teilchengröße von 50 µm oder mehr, vorzugsweise 75 µm oder mehr aufweisen.

6. Verfahren zur Herstellung eines rieselfähigen verpressbaren Stärkepulvers, welches die Schritte umfasst: 1) Herstellen einer Aufschlämmung von Stärke in Wasser, 2) Erwärmen der Aufschlämmung auf eine Temperatur, welche nicht wesentlich höher ist als die Verkleisterungstemperatur der Stärke, um ein partielles Quellen der Stärkegranalien zu verursachen, ohne ein Zerbrechen der Stärkegranalien zu verursachen, 3) Abkühlen der Stärkeaufschlämmung, um jedes weitere Quellen der Stärkegranalien zu verhindern, und 4) Sprühtrocknen der abgekühlten Aufschlämmung, um ein rieselfähiges Stärkepulver mit einem Feuchtigkeitsgehalt von 3 bis 15 Gewichts-% zu erzeugen.

7. Verfahren nach Anspruch 6, in dem die Aufschlämmung auf eine Temperatur erwärmt wird, die ± 5°C der Verkleisterungstemperatur der Stärke, vorzugsweise ± 1°C der Verkleisterungstemperatur der Stärke beträgt.

8. Verfahren nach Anspruch 6 oder Anspruch 7, in dem die Stärkeaufschlämmung nach dem Erwärmungsschritt auf eine Temperatur abgekühlt wird, die 5 bis 15°C niedriger ist als die Temperatur, die in dem Erwärmungsschritt verwendet wurde.

9. Zusammensetzung zur Bildung einer Tablette oder einer anderen Dosierungseinheit-Form, die mindestens ein aktives Material und als Bindemittel oder Füllstoff ein rieselfähiges direkt verpressbares verarbeitetes Stärkepulver nach irgendeinem der Ansprüche 1 bis 5 umfasst.

10. Zusammensetzung nach Anspruch 9, in der das aktive Material aus der Gruppe ausgewählt ist, die aus pharmazeutisch aktiven Materialien, Nahrungsmitteln, einschließlich Konfektprodukten, Aromas oder Süßungsmitteln, Detergentien, Enzymen und anderen Proteinen, Farbstoffen, Düngemitteln und herbiziden Produkten besteht.

11. Trocken verpresste Tablette, umfassend mindestens ein aktives Material und als Bindemittel oder Füllstoff verarbeitete Stärke, wobei die verarbeitete Stärke regelmäßige und glatte partiell gequollene Granalien aus Stärke umfasst, wobei das Verhältnis von nicht-gequollenen doppelbrechenden Granalien zu gequollenen nicht-doppelbrechenden Granalien im Bereich von 1:5 bis 5:1 liegt und diese eine durchschnittliche Teilchengröße von mehr als 50 µm und einen Feuchtigkeitsgehalt im Bereich von 3 bis 15 Gewichts-% aufweisen, wobei die Tablette, wenn sie unter einer Kompressionskraft von 15 kN geformt wird, eine Zugfestigkeit von mehr als 2 N/mm^2, vorzugsweise mehr als 3 N/mm^2 und bevorzugter mehr als 4 N/mm^2, eine Zerfallszeit in Wasser bei 37°C von weniger als 6 Minuten und eine prozentuale Brüchigkeit von weniger als 1% aufweist.

Revendications

1. Une poudre d'amidon traitée s'écoulant librement et directement compressible, **caractérisée en ce qu**'elle comporte des granules d'amidon réguliers et homogènes partiellement gonflés avec un rapport de granules biréfringents non gonflés / granules gonflés non biréfringents de 1/5 à 5/1, et **en ce qu**'elle a une granulométrie moyenne supérieure à 50 µm et une teneur en humidité de 3% à 15% en poids, et, lorsqu'elle est comprimée avec une force 10 kN pour produire un comprimé, ladite poudre d'amidon traitée s'écoulant librement, directement compressible, produit un comprimé dont la résistance à la traction est d'au moins 1 N/mm^2.

2. Une poudre d'amidon traitée s'écoulant librement et compressible selon la revendication 1, **caractérisée en ce que** le comprimé a une résistance à la traction d'au moins 2 N/mm^2.

3. Une poudre d'amidon traitée s'écoulant librement et compressible selon l'une quelconque des revendications 1 ou 2, **caractérisée en ce que** le ratio de granules biréfringents non gonflés /granules non biréfringents partiellement gonflés est de l'ordre de 1/2 à 2/1.

4. Une poudre d'amidon traitée s'écoulant librement et compressible selon l'une quelconque des revendications précédentes, **caractérisée en ce que** le ratio de granules biréfringents non gonflés /granules non biréfringents partiellement gonflés est d'environ 1/1.

5. Une poudre d'amidon traitée s'écoulant librement et compressible selon l'une quelconque des revendications précédentes, **caractérisée en ce que** au moins 50% des particules ont une granulométrie d'au moins 50 µm , et, de

préférence, d'au moins 75 µm.

6. Un procédé de préparation d'une poudre d'amidon s'écoulant librement et compressible, comprenant les étapes : 1) préparation d'une pâte d'amidon dans l'eau, 2) chauffage de la pâte jusqu'à une température à peine plus élevée que la température de gélatinisation de l'amidon afin de provoquer un gonflement partiel des granules d'amidon sans éclatement, 3) refroidissement de la pâte d'amidon afin d'empêcher tout autre gonflement des granules d'amidon et 4) atomisation de la pâte refroidie afin de produire une poudre d'amidon s'écoulant librement, présentant une teneur en humidité de 3% à 15% en poids.

7. Un procédé selon la revendication 6, **caractérisé en ce que** la pâte est chauffée à une température de ±5°C de la température de gélatinisation de l'amidon, de préférence ±1°C de la température de gélatinisation de l'amidon.

8. Un procédé selon l'une quelconque des revendications 6 ou 7, **caractérisé en ce que**, après chauffage, la pâte d'amidon est refroidie jusqu'à une température de 5°C à 15°C inférieure à la température utilisée à l'étape de chauffage.

9. Une composition permettant de former un comprimé ou une autre forme posologique comprenant au moins une matière active et, comme liant ou charge, une poudre d'amidon traitée s'écoulant librement et directement compressible selon l'une quelconque des revendications 1 à 5.

10. Une composition selon la revendication 9, **caractérisée en ce que** la matière active est choisie parmi le groupe comportant des matières pharmaceutiquement actives, des aliments, y compris des produits de confiserie, des arômes ou des édulcorants, des détergents, des enzymes et autres protéines, des colorants, des engrais et des herbicides.

11. Un comprimé par compression à sec, comprenant au moins une matière active et, comme liant ou charge, de l'amidon traité, ledit amidon traité comportant des granules d'amidon réguliers et homogènes partiellement gonflés, où le ratio de granules biréfringents non gonflés / granules non biréfringents gonflés est de l'ordre de 1/5 à 5/1, ayant une granulométrie moyenne de plus de 50 µm et une teneur en humidité de l'ordre de 3% à 15% en poids, ledit comprimé, lorsque formé avec une force de compression de 15 kN, ayant une résistance à la traction de plus de 2 N/mm^2, de préférence supérieure à 3 N/mm^2 et de préférence supérieure à 4 N/mm^2, un temps de désintégration dans l'eau à 37°C inférieur à 6 minutes et un pourcentage de friabilité inférieur à 1%.

PARTIALLY SWOLLEN WHITE MAIZE STARCH GRANULES

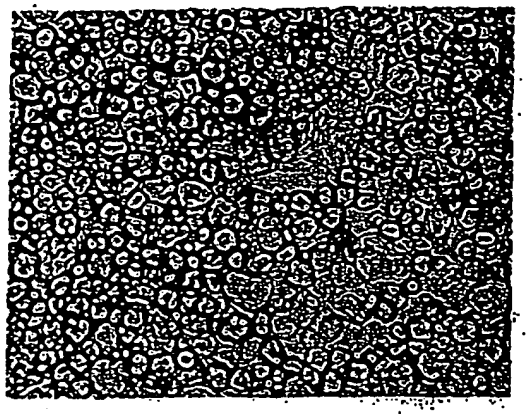

Fig. 1 Partially swollen white maize starch at 61°C

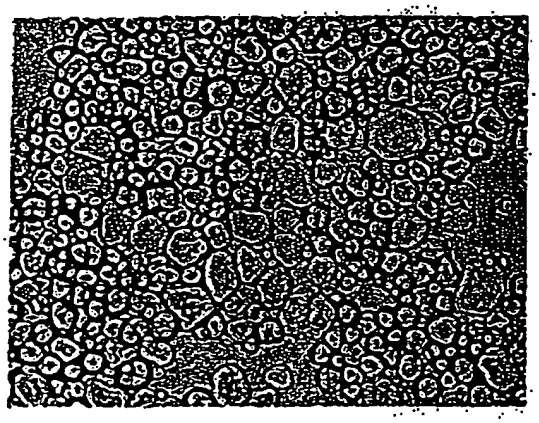

Fig. 2 Partially swollen white maize starch at 62°C

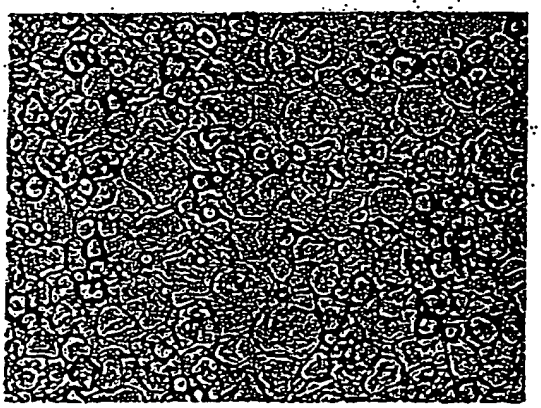

Fig. 3 Partially swollen white maize starch at 63°C

S.E.M. PICTURES OF STARCHES

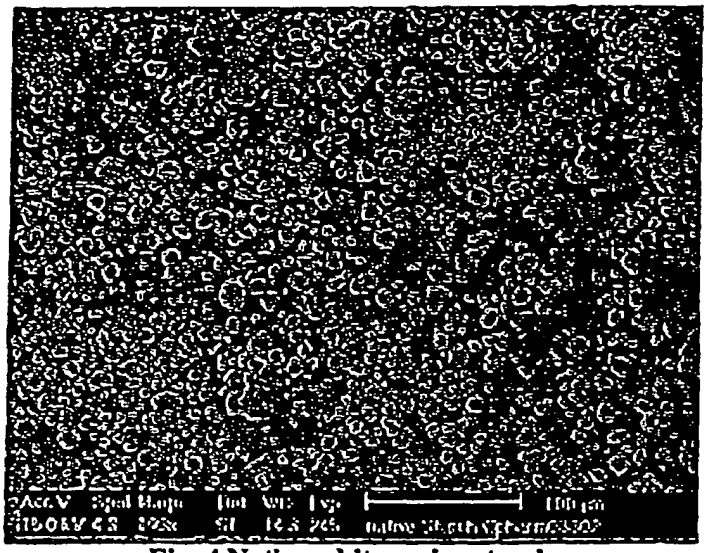

Fig. 4 Native white maize starch

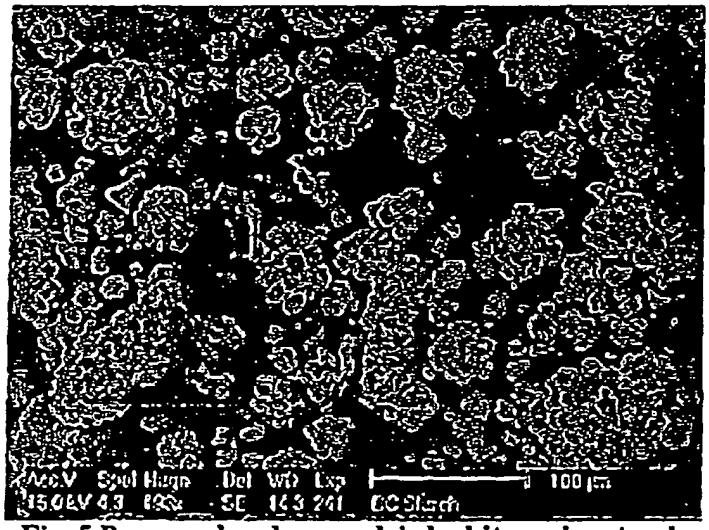

Fig. 5 Processed and spray-dried white maize starch